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⑯ Pharmaceutical composition containing urokinase.

⑯ A pharmaceutical composition containing urokinase and a physiological absorption enhancer comprising higher fatty acids, a polyalkylene glycol and calcium is disclosed. Where, as urokinase which is decomposed and inactivated in the stomach and is poorly absorbed from the intestinal tract cannot be orally administered, it can be orally administered in the form of the present composition by applying enteric coating, because urokinase in the composition is highly absorbable from the intestinal tract. It is desirable in the present composition in view of the stability and sustained absorbability that urokinase is contained in said composition in the form of a liposome preparation in which the urokinase is incorporated in voids of the liposome. The components are incorporated in the present composition at a ratio of 0.01 - 2 mg. of the higher fatty acid, 0.01 - 5 mg. of the polyalkylene glycol and 0.0001 - 0.1 mg. of the calcium per 100 units of urokinase. The present composition is satisfactory for use as a thrombolytic agent.

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Title of the Invention

Pharmaceutical composition containing urokinase

Background of the Invention

1. Field of the Invention

5 The present invention relates to a pharmaceutical composition containing urokinase improved in intestinal absorption.

More particularly, it is concerned with a pharmaceutical composition containing urokinase improved in 10 intestinal absorbability comprising urokinase and a physiological absorption enhancer.

Urokinase is a fibrinolytic and thrombolytic enzyme. Clinically, it is useful as a thrombolytic agent for a variety of thrombosis such as cerebrovascular obstruction, myocardial infarct and pulmonary embolism. It is 15 also used in combination with antitumor agents.

2. Prior Arts

The route of administration of drugs is classified into divisions such as injectable, oral and topical ones. Except for special cases, the oral administration is more useful than parenteral one in view of the 20 troubles of patient, physician and other persons concerned as well as patients suffering so far as the same result is produced.

When orally administered, urokinase is decomposed and inactivated in the stomach by the actions of such substances as proteases and a gastric acid. Moreover, it is poorly absorbed from the intestinal tract. Heretofore, it has been administered by intravenous injection or by intravenous infusion. Although urokinase can be administered by these routes of administration without decomposition and inactivation, they are unsatisfactory in that each administration has to be exercised by a physician and the patient suffers pain.

In addition, as urokinase has a half life in blood as short as approximately 15 min., maintaining urokinase in blood at a given level is difficult and effect of the drug is not durable.

15 Summary of the Invention

It is an object of the present invention to provide a pharmaceutical composition containing urokinase highly absorbable from the intestinal tract.

Another object of the invention is to provide a pharmaceutical composition containing urokinase improved in intestinal absorbability which is slowly adsorbed and produces durable effects.

In order to achieve the above-mentioned objects the pharmaceutical composition of the invention improved

in intestinal absorbability comprises urokinase and a physiological absorption enhancer.

Brief Description of the Drawings

Fig. 1 of the accompanying drawings is a graph indicating the urokinase activity in plasma (I. U./mL.) following gastric administration of enteric coating capsule containing a composition of the invention according to Example 1 or 3 or a control composition. Fig. 2 is a graph indicating α_2 -PI activity in plasma (%) following gastric administration of enteric coating capsule containing a composition of the invention according to Example 1 or 3 or a control composition. Fig. 3 is a graph indicating changes of α_2 -PI activity in plasma following gastric or intravenous administration in rats of a composition of the invention according to Example 4 or a control composition, and Fig. 4 is a graph indicating changes of α_2 -PI in plasma following intraduodenal or intravenous administration in dogs of a composition of the invention according to Example 4 or a control composition.

Detailed Description of the Invention

As described above, urokinase, when orally administered, is decomposed and inactivated in the stomach.

Even if the decomposition and inactivation in the stomach is prevented by such a means as the enteric coating, efficiency of the absorption from the intestinal tract is low.

5 As a result of extensive studies we have found that, unexpectedly, combination of urokinase with higher fatty acids, polyalkylene glycols and calcium results in an efficient absorption of the urokinase from the intestinal tract by oral administration with a high blood 10 level maintained for a long period of time. The present invention is based upon the above finding.

Accordingly, the invention relates to a pharmaceutical composition containing urokinase improved in 15 intestinal absorbability comprising a therapeutically effective amount of urokinase, and an effective amount of physiological absorption enhancer, said enhancer comprising one or more higher fatty acids, a polyalkylene glycol and calcium.

Any of the urokinases which are pharmaceutically 20 acceptable may be used in the invention. Usually, human-origin urokinases with a molecular weight in the range from 25,000 to 60,000 are employed.

Urokinase contained in the composition of the invention may be in natural form or in the form of an 25 urokinase-carrying liposome preparation in which the

urokinase is incorporated into innerspace of small lipid particles (liposome). When urokinase is contained in the composition of the invention in the form of a liposome preparation, lipids particularly phospholipids

5 suitable for forming liposome are employed as the membrane material for the liposome. As the phospholipid may used any of natural and synthetic phospholipids and hydrogenated derivatives of natural phospholipids. As all of the phospholipids contain unsaturated fatty acids,

10 it is more effective to employ hydrogenated phospholipids in which the unsaturated fatty acids in natural phospholipids are saturated with hydrogen. Synthetic phospholipids may also be employed, but presently they are too expensive to justify economic consideration.

15 As typical examples of the phospholipid used in the invention are mentioned soybean lecithine, yolk lecithine, corn lecithine, cotton seed oil lecithine, rape lecithine, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, phosphatidyl-

20 glycerol, sphingomyelin, cardiolipin and the like. In addition, hydrogenated derivatives of these phospholipids prepared by conventional procedures are also mentioned. Especially preferred are hydrogenated derivatives of natural phospholipids from hydrogenation

25 of soybean, yolk, corn, cotton seed oil or rape lecithine.

Use of the hydrogenated lecithine enables slower absorption of the urokinase from the intestinal tract with a longer duration of the drug efficacy.

In order to enhance strength of the membrane a 5 sterol such as cholesterol or tocopherol may be added to the membrane material according to the present invention. Sustained release of the drug in the body can be adjusted by the addition of a substance giving negative electric charge such as, for example, phosphatidic acid 10 or dicetylphosphate. Degradation of the liposomal membrane is controlled by the presence of such substance.

The urokinase-carrying liposome preparation of the invention is prepared by a method known per se. For example, a natural phospholipid or a hydrogenated 15 derivative of natural phospholipid and, if desired, a sterol and a substance giving negative electric charge are dissolved in an appropriate solvent such as chloroform or ethanol; an aqueous solution of urokinase is added to the solution; the resulting mixture is vigorously shaken to give a homogeneous dispersion of the aqueous drug solution; and the solvent is distilled off the dispersion to give an urokinase-carrying liposome 20 preparation. The liposome preparation thus obtained is washed with a physiologically acceptable aqueous 25 solution such as physiological saline solution and then

formed into pellets, granules or powders.

Lyophilization of the urokinase-carrying liposome preparation of the invention can be carried out under conventional conditions. For example, it is preferably 5 done by freezing the preparation at -20 to -80°C. and subliming the ice under a reduced pressure at or below 0.3 torr. In order to form a good lyophilized cake, a conventional excipient such as mannitol, dextrin or glycine may be added.

10 Preferable higher fatty acids used in the invention are those which contain 10 - 20 carbon atoms, examples of which include capric, lauric, myristic, palmitic, stearic, oleic, linolic, linolenic and arachidonic acids. Especially preferred are unsaturated higher fatty acids 15 containing 1 - 4 double bonds and 18 - 20 carbon atoms, for example, oleic, linolic, linolenic and arachidonic acids. Oleic acid is most preferable. These higher fatty acids may be used alone or in combination.

As examples of the polyalkylene glycols in the 20 invention are mentioned polyethylene glycol and polypropylene glycol. Degree of polymerization of the polyalkylene glycol is preferably in the range between 5 and 500. Polyethylene glycol of a degree of polymerization of 160 - 200 is especially preferred.

25 The calcium in the present invention is used in

the form of a compound acceptable as a component of pharmaceutical formulations. For example, it is contained in the composition according to the invention in the form of calcium chloride, lactate, phosphate or gluconate.

5 Part of the above-mentioned higher fatty acid may be contained in the membrane material of liposome in the urokinase-containing liposome preparation of the invention.

10 By incorporating the higher fatty acid into the membrane structure of the membrane can be changed so as to enlarge voids in the liposome as compared with those in the absence of the higher fatty acid. Moreover, as the higher fatty acid in the membrane is also released when the liposome is degraded, a synergistic absorption-15 promoting effect is produced in combination with the higher fatty acid separately present in the voids.

15 Amount of the higher fatty acid incorporated in the membrane is preferably at such a concentration that it is 5% by weight or higher but no micelle of the phospholipid is formed. When concentration of the higher fatty acid incorporated is 5% by weight or higher, and preferably 10% by weight or higher, there are produced results satisfactory for the objects of the invention in affinity, stability, sustained release and 25 other properties. The concentration should be in such

a range that the phospholipid remains in lamella structure. Otherwise, it will not be able to carry the drug in the liposome. Higher concentrations of the higher fatty acid incorporated will result in formation of 5 micelles in which the phospholipid will contain the higher fatty acid at the center with no liposome formed. In such a case, amount of the higher fatty acid incorporated will reach about 30% by weight, though it is variable depending upon the conditions. Therefore, 10 unless the higher fatty acid is incorporated at a concentration below the one defined above, no liposome will be formed so that efficiency of carrying the drug will be extremely low or impossible. Preferably, the concentration is 15% by weight or lower. As the amount 15 of the higher fatty acid to be incorporated in the liposome membrane is not sufficient to achieve the objects of the invention, it is desired to add the above-mentioned higher fatty acid as a separate component of the composition.

20 The ratio of urokinase, higher fatty acids, poly-alkylene glycols and calcium to be incorporated in the composition of the invention is from 0.02 to 2 mg., preferably from 0.05 to 0.5 mg. of the higher fatty acids, from 0.01 to 5 mg., preferably from 0.1 to 1 25 mg. of the polyalkylene glycols and from 0.0001 to 0.1

mg., preferably from 0.0005 to 0.005 mg. of calcium per 100 units of urokinase, although it is not critical.

The composition of the present invention is formulated for oral or rectal administration by conventional procedures. Tablets, capsules or suppositories are prepared by adding as needed, diluents such as calcium carbonate, calcium phosphate, talc, lactose, dextran and starch, binders such as arabic gum and tragacanth powder, lanolin and coconut oil. Since urokinase is decomposed and inactivated with gastric juice, it is desirable to apply enteric coating to the above-described tablets or capsules by conventional procedures using, for example, hydroxypropylmethylcellulose phthalate.

Content of urokinase per tablet, capsule or suppository is adequately determined in accordance with the dosage of urokinase. For example, urokinase is administered at a daily dose of at least 100,000 - 500,000 units for the treatment of thrombosis, for which it is desirable to contain 30,000 - 120,000 units of urokinase per tablet, capsule or suppository.

The present invention will be described below in more details with reference to examples and test examples.

Example 1.

(1) Preparation of urokinase-carrying liposome powders.

Hydrogenated lecithine, cholesterol and dicetyl phosphate are blended at a molar ratio of 7:7:1. In a 50-ml. egg plant-form flask is placed a solution of 50.6 mg. of the blend in 15 ml. of chloroform. The solvent 5 is distilled off by means of a rotary evaporator to form a thin film on the inner surface of the flask. Then, there is added 6 ml. of 1:1 (volume) mixture of chloroform : isopropylether to dissolve the film, followed by addition of 1 ml. of phosphate buffer (pH 7.2, 0.1M) 10 containing 180,000 units of urokinase. The resulting mixture is subjected to an ultrasonic treatment in a ultrasonic cleaner of water-bath type at 4°C. for 5 min. to a homogeneous dispersion. The solvent is distilled at 40°C. off the dispersion by means of a rotary evapo- 15 rator until gel is formed. To the gel is added 5 ml. of physiological solution, and the mixture is stirred. Distillation of the solvent is continued for additional 10 min. to give a liposome suspension. The suspension is centrifuged at 100,000 G for 60 min. and washed with 20 two portions of physiological saline solution. The pellets thus obtained are suspended in physiological saline solution and subjected to a sterilization treat- ment to give an urokinase-carrying liposome. The urokinase-carrying liposome is lyophilized to obtain 25 powdered urokinase-carrying liposome.

(2) Preparation of the composition of the invention.

To a suspension of 35 mg. of oleic acid in an aqueous solution of hardened castor oil are added 100 mg. of polyethylene glycol 6000 and 0.7 mg. of calcium chloride to a solution, which is lyophilized to give powders. The powders are blended with the powdered urokinase-carrying liposome to give a composition of the invention. The composition in admixture with an appropriate amount of polyethylene glycol and dextran are filled in a gelatin capsule to give an urokinase capsule preparation.

Example 2.

The powdered urokinase-carrying liposome (containing 60,000 units) prepared according to Example 1 (1) is mixed with powders composed of 35 mg. of oleic acid, 100 mg. of polyethylene glycol 6000 and 0.7 mg. of calcium chloride to prepare a composition of the invention. The composition in admixture with an appropriate amount of starch, lactose and arabic gum is tableted and subjected to enteric coating to give urokinase tablets.

Example 3.

To 10 ml. of an aqueous solution containing 60,000

units of urokinase is added 50 mg. of polyethylene glycol 6000. The mixture is stirred to give a solution, which is lyophilized. The lyophilized mass is blended with powders composed of 35 mg. of oleic acid, 50 mg. of polyethylene glycol 6000 and 0.7 mg. of calcium chloride. The blend in admixture of an appropriate amount of polyethylene glycol and dextran is filled in a gelatin capsule, which is subjected to enteric coating to give a urokinase capsule preparation.

10 Test Example 1.

Absorption test by gastric administration

Wister male rats weighing 200 - 250 g. were administered into the stomach respectively with an urokinase capsule preparation of the invention prepared according to Example 1 (10,000 units, referred to as Capsule 1 hereinbelow), an urokinase composition of the invention prepared according to Example 3 (10,000 units, referred to as Capsule 2 hereinbelow) and a control capsule preparation of urokinase alone without higher fatty acid, polyalkylene glycol and calcium contained (10,000 units, referred to as Capsule 3 hereinbelow). Blood was drawn from the animals after predetermined periods of time and measured for the blood urokinase level using a synthetic substrate S-2444. Results are graphically

shown in Fig. 1.

In Fig. 1, the line with closed circles indicates urokinase activity (I. U./mL.) in plasma when Capsule 1 was administered (average in 10 animals), the line with 5 closed triangles when Capsule 2 was administered (average in 10 animals) and the line with open circles when Capsule 3 was administered (average in 10 animals).

As shown in Fig. 1, the blood level of urokinase was rapidly increased in about 1 hour after administration 10 of Capsule 1 or Capsule 2, and maintained thereafter over 6 hours or longer. On the contrary, the blood level after administration of Capsule 3 was rapidly increased in about 1 hour but was rapidly decreased thereafter with no duration observed.

15 Test Example 2.

Absorption test by intraduodenal (referred to as i.d. hereinbelow) administration

Healthy beagle dogs (7 - 8 months old) weighing 9 - 13 Kg. were administered by i.d. route respectively 20 with an urokinase capsule preparation of the invention prepared according to Example 1 (30,000 units, referred to as Capsule 4 hereinbelow), an urokinase capsule preparation of the invention prepared according to Example 3 (30,000 units, referred to as Capsule 5

hereinbelow) and a control capsule preparation of urokinase alone without higher fatty acid, polyalkylene glycol and calcium contained (30,000 units, referred to as Capsule 6 hereinbelow). Blood was drawn from the 5 animals after predetermined periods of time and measured for blood α_2 -PI (α_2 -plasmin inhibitor) activity using a synthetic substrate S-2251. Results are graphically shown in Fig. 2.

In Fig. 2, the line with closed circles indicates 10 α_2 -PI activity (%) in plasma when Capsule 4 was administered (average in 10 animals), the line with closed triangles when Capsule 5 was administered (average in 10 animals) and the line with open circles when Capsule 6 was administered (average in 10 animals).

15 As shown in Fig. 2, the α_2 -PI activity was rapidly decreased in about 30 min. after administration of Capsule 4 and maintained thereafter for approximately 10 hours. It was rapidly decreased also with Capsule 5 and maintained for approximately 6 hours. On the 20 contrary, the α_2 -PI activity after administration of Capsule 6 was rapidly decreased in about 30 min. but returned rapidly to normal level with no duration observed.

As clearly seen from Test Examples 1 and 2 above, 25 the urokinase composition according to the present

invention is associated with increase in the efficiency of absorption and duration of the efficacy of the drug as compared with urokinase alone.

Example 4.

5 (1) Preparation of a powdered urokinase liposome with a higher fatty acid added.

In 3 ml. of chloroform were dissolved 32 mg. of lecithine, 15.4 mg. of cholesterol and 5 mg. of oleic acid. The solution was placed in a 50-ml. egg plant-form flask, to which 3 ml. of isopropylether was added. The mixture was stirred to a blend, to which 1 ml. of an aqueous solution containing 10,000 units of urokinase was added. The resulting mixture was subjected to a sonication at 4°C. for 5 min. in an ultrasonicator of water-bath type to a homogeneous dispersion. The solvent was evaporated by means of a rotary evaporator until gel was formed. The gel was stirred with 5 ml. of physiological saline solution. Evaporation of the solvent was then continued for additional 10 min. to give a liposome suspension. The suspension was centrifuged at 100,000 G for 30 min. and washed with two portions of physiological saline solution. The pellets thus obtained were suspended in physiological saline solution and subjected to a sterilization treatment to

give an urokinase liposome. The urokinase liposome was lyophilized to give a powdered urokinase liposome.

(2) Preparation of an absorption enhancer.

To 35 mg. of oleic acid was added 0.5 mg. of HCO-60
5 (polyoxyethylene-hydrogenated castor oil). The mixture was stirred to a blend, to which was 100 mg. of polyethylene glycol 6000 with 5 ml. of water. The mixture was vigorously stirred to give a homogeneous suspension, to which was then added 0.7 mg. of calcium chloride.
10 After dissolved, the solution was lyophilized to give a powdered absorption enhancer.

(3) Preparation of the composition of the invention

(3-1) To a mixture of the powdered urokinase liposome (containing 60,000 units of urokinase and 136 mg. of
15 the powdered absorption enhancer respectively prepared in (1) and (2) above was added an appropriate amount of polyethylene glycol and dextran. The resulting mixture was filled in a gelatin capsule, to which was applied enteric coating.
20 (3-2) To a mixture of the powdered urokinase liposome (containing 30,000 units of urokinase) and 136 mg. of the powdered absorption enhancer respectively prepared in (1) and (2) above was added an appropriate amount of starch, lactose and hydroxypropylcellulose. The
25 resulting mixture was tableted, and enteric coating was

applied to the tablet.

Then, the following tests were run in order to confirm the effect of the urokinase composition improved in enteric absorbability according to the present invention.

5 Test Example 3.

Absorption test by gastric administration

Capsule 7 which was an urokinase-liposome composition of the invention prepared according to Example 4 (3-1) and a lyophilized preparation commercially available were employed.

10 Wister male rats weighing 200 - 250 g. were administered each with 10,000 units of urokinase by gastric route for the capsule preparation of the invention or by gastric route or intravenously for the commercial preparation. Blood was drawn at intervals and assayed for the α_2 -PI (α_2 -plasmin inhibitor) activity using a synthetic substrate S-2251.

15 Results are shown in Fig. 3. The commercial preparation, when administered into the stomach, was absorbed to a very low extent to induce almost no decrease in the α_2 -PI activity. When administered intravenously, there was observed a rapid decrease in the activity, which was rapidly recovered with no duration observed. On the other hand, administration of Capsule 7 of the

invention induced a decrease to approximately 60% after 1 hour, which was lasted over 6 hours or longer.

Test Example 4.

Absorption test by intraduodenal administration

5 Capsule 8 which was an urokinase-liposome preparation of the invention prepared according to Example 4 (3-1) and a lyophilized preparation commercially available were employed. Healthy beagle dogs weighing 9 - 13 Kg. were administered each with 60,000 units of urokinase 10 by duodenal route for the capsule preparation of the invention or by duodenal route or intravenously for the commercial preparation. Blood was drawn at intervals and assayed for the α_2 -PI (α_2 -plasmin inhibitor) using a synthetic substrate S-2251.

15 Results are shown in Fig. 4. The commercial preparation, when administered into the duodenum, was absorbed to a very low extent to induce no decrease in the α_2 -PI activity. When administered intravenously, there was observed a rapid decrease in the activity, which 20 was rapidly recovered with no duration observed. On the other hand, administration of Capsule 8 of the invention induced a decrease to a maximum value of 65% in one hour, which was lasted over 10 hours or longer.

In Figs. 3 and 4, the line with open circles

indicates the results with Capsule 7 or 8 of the invention and the lines with open squares indicate the results with the commercial preparation respectively when administered into the stomach (Fig. 3) or the duodenum (Fig. 5 4). The line with open triangles indicates the results with the commercial preparation when administered intravenously. The results are each an average of the values obtained in 10 animals.

According to the present invention, there is provided an urokinase composition which can be administered by enteric route. As described above, whereas urokinase alone is absorbed from the intestinal tract only to a very low extent, combination of urokinase with higher fatty acids, polyalkylene glycols and calcium significantly increase the enteric absorption of urokinase. 10 15

Also according to the invention, an urokinase composition with which the efficacy of urokinase is lasting is provided. Since urokinase is quickly decomposed in blood, it is difficult for the prior-art method of 20 administration to achieve a duration of the efficacy for a long period of time.

On the other hand, the urokinase in the composition of the invention is slowly absorbed from the intestinal tract to enable maintaining a high blood level of 25 urokinase for a long period of time, which in turn

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enables the efficacy to last. Especially, when urokinase is used in the form of an urokinase-carrying liposome, duration of the efficacy will be longer.

What is claimed is:

1. A pharmaceutical composition containing urokinase comprising a therapeutically effective amount of urokinase and an effective amount of physiological absorption enhancer, said enhancer comprising one or more higher fatty acids, a polyalkylene glycol and calcium.
2. A pharmaceutical composition containing urokinase according to Claim 1 wherein the higher fatty acid contains 10 - 20 carbon atoms.
3. A pharmaceutical composition containing urokinase according to Claim 2 wherein the higher fatty acid contains 1 - 4 double bonds and 18 - 20 carbon atoms.
4. A pharmaceutical composition containing urokinase according to Claim 3 wherein the higher fatty acid is oleic acid.
5. A pharmaceutical composition containing urokinase according to Claim 3 wherein the polyalkylene glycol is a polyethylene glycol.

6. A pharmaceutical composition containing urokinase according to Claims 1 - 5 wherein the urokinase is an urokinase-carrying liposome preparation.

7. A pharmaceutical composition containing urokinase according to Claim 6 wherein the urokinase-carrying liposome preparation is a liposome preparation the membrane material of which contains a lipid and a higher fatty acid.

8. A pharmaceutical composition containing urokinase according to Claim 6 or 7 wherein the lipid is a hydrogenated lecithine.

9. A pharmaceutical composition containing urokinase according to Claim 1 which contains 0.01 - 2 mg. of the higher fatty acid, 0.01 - 5 mg. of the polyalkylene glycol and 0.0001 - 0.1 mg. of the calcium per 100 units of the urokinase.

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Fig. 1

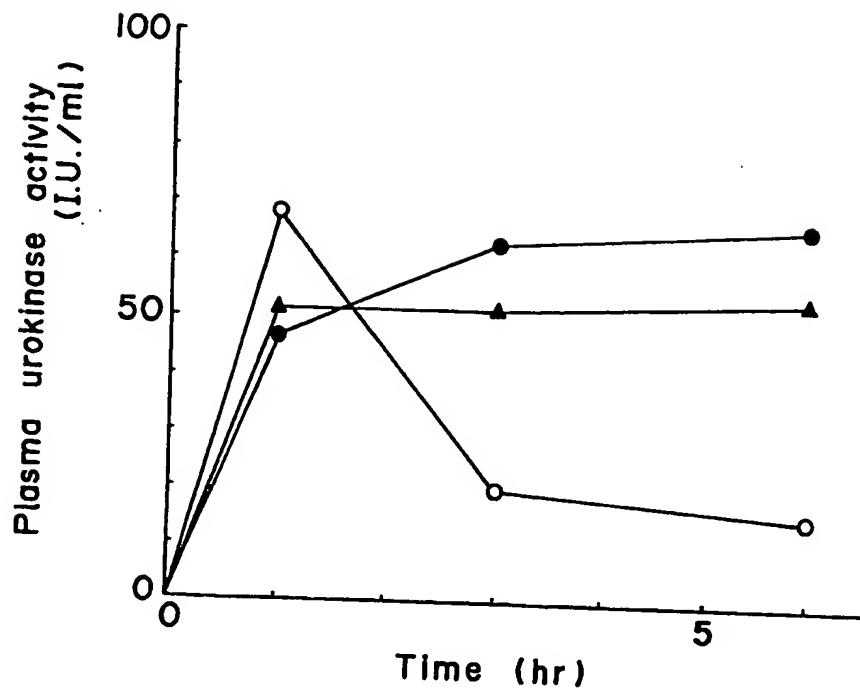
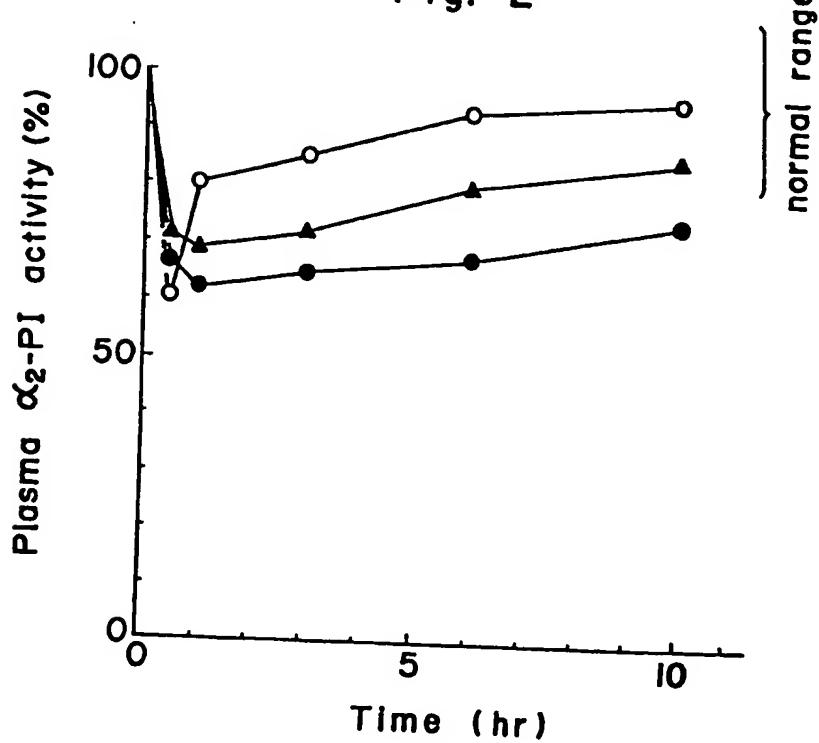


Fig. 2



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Fig. 3

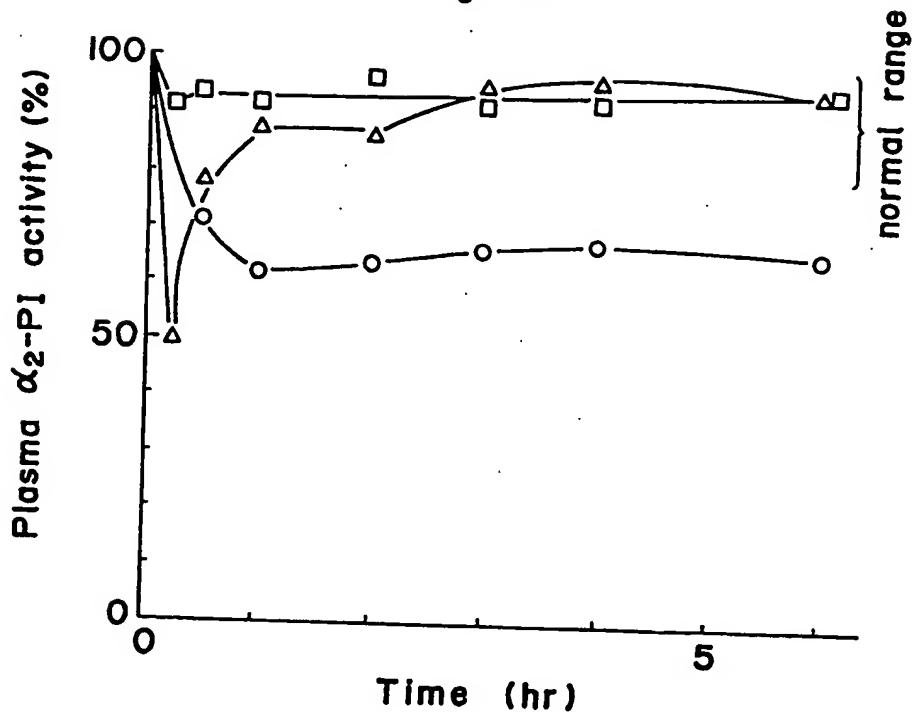
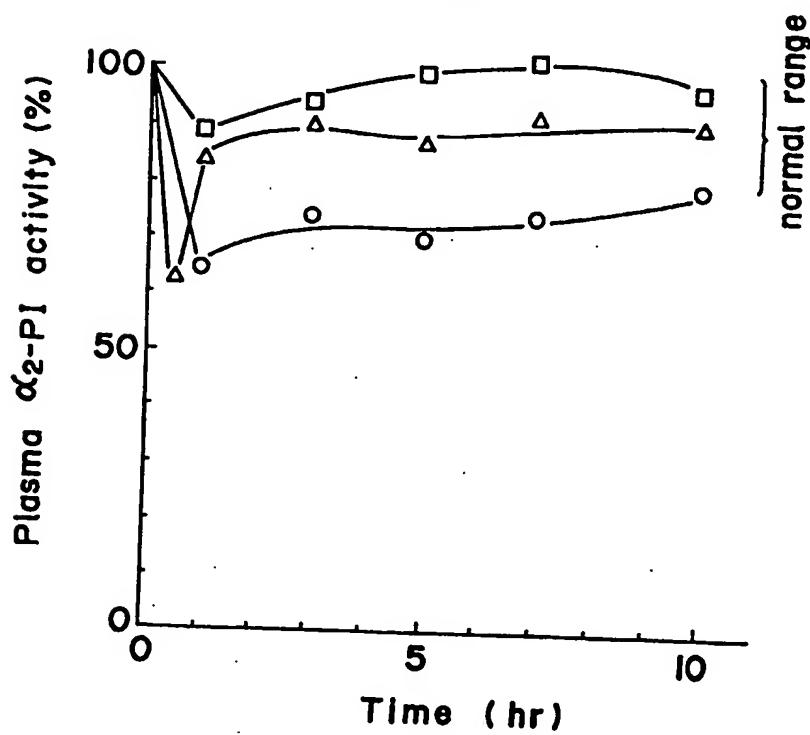


Fig. 4





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EUROPEAN SEARCH REPORT

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Application number

EP 84 11 2090

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CHEMICAL ABSTRACTS, vol. 96, no. 20, 17th May 1982, page 403, no. 168735z, Columbus, Ohio, US; & JP - A - 82 04 913 (GREEN CROSS CORP.) 11-01-1982 * abstract *	1-9	A 61 K 37/547 A 61 K 9/50
A	--- CHEMICAL ABSTRACTS, vol. 96, no. 16, 19th April 1982, page 460, no. 129726c, Columbus, Ohio, US; R.F. SCHMELTER et al.: "A preliminary study of the association of urokinase with liposomes" & CAN. J. PHARM. SCI. 1981, 16(1), 37-9 * abstract *	1-9	
	-----		TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K
<p>The present search report has been drawn up for all claims</p>			
Place of search THE HAGUE	Date of completion of the search 30-01-1985	Examiner BRINKMANN C.	
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			